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EXAMINER
BRISTOL, LYNN ANNE

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

	Application No.	Applicant(s)
Office Action Summary	10/510,971	KOJIMA, TETSUO
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.
- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2009*.
2a)☐ This action is **FINAL**.   2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-22,31-34,43 and 44* is/are pending in the application.
    4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *19-22,31-34,43 and 44* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
    Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
    Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
    a)☐ All   b)☐ Some * c)☐ None of:
        1.☐ Certified copies of the priority documents have been received.
        2.☐ Certified copies of the priority documents have been received in Application No. _____.
        3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
    * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
    Paper No(s)/Mail Date *1/13/09*.
4) ☐ Interview Summary (PTO-413)
    Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____ .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1.   A request for continued examination under 37 CFR 1.114, including the fee set

forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this

application is eligible for continued examination under 37 CFR 1.114, and the fee set

forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action

has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/13/09

has been entered.

2.   Claims 19-22, 31-34, 43 and 44 are all the pending claims for this application and

all the claims under examination.

3.   Claims 23-30, and 35-42 were cancelled and Claims 19, 21, 31, 33, and 43 were

amended in the Response of 1/13/09.

4.   This Office Action contains new grounds for rejection.

Information Disclosure Statement

5.   The information disclosure statement filed 1/13/09 has been considered and

entered. The examiner's initialed copy of the 1449 form from the IDS is attached.

<u>*Withdrawal of Rejections*</u>

Claim Rejections - 35 USC § 112

Enablement

6.   The rejection of Claims 19-44 under 35 U.S.C. 112, first paragraph, is lacking

enablement for producing any of the foregoing libraries from unpaired single variable

domains where the domains are from different antibodies against the same antigen or

different antibodies against different antigens is withdrawn.

Applicants' claim amendments, their comments on pp. 15-16 of the Response of

1/13/09 and the Clarkson et al. reference (Nature 352:624-628 (1991); Exhibit C) have

been considered and are found persuasive in overcoming the rejection. The claims have

been amended to clarify and meet the definition for a diabody much less that each of the

first and second single chain antibodies comprising the diabody would have the ability to

bind a first and second antigen, respectively.

Claim Rejections - 35 USC § 103

7.   The rejection of Claims 19-22, 31-34, 43 and 44 under 35 U.S.C. 103(a) as being

unpatentable over McGuinness et al. (Nat. Biotech. 14:1149-1154 (1996); cited in the

PTO 892 form of 8/8/07) and Volkel (Protein Engineering 14(10):815-823 (2001); cited

in the IDS of 5/25/06) is withdrawn.

Applicants allegations on pp. 16-21 of the Response of 1/13/09 have been

considered and are found persuasive. Applicants have amended the claims to more

clearly recite the method steps and the specific insertion scheme for generating the

library for the diabody. Applicants allege "McGuinness does not disclose inserting a

sequence encoding a second pair of heavy and light chain variable domains into the

open restriction site, and does not disclose generating a construct encoding a single

polypeptide chain comprising all four variable domains, all as required by step (e)" and

"Vokkel started with a known single chain diabody construct containing four variable

domains (pAB 1 scDb CEAGal), not a pair of libraries, each member of which encodes

two variable domains, as required by steps (a) and (b) of claim 19."

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

8.   The rejection of Claims 19-22, 31-34, 43 and 44 under 35 U.S.C. 112, first

paragraph, as failing to comply with the written description requirement is maintained

For purposes of review, the rejection was set forth in the Office Action of 4/15/08

as follows:

"Claims 19-30 are interpreted as being drawn to methods for constructing a single chain diabody library, Claims 31-42 are interpreted as being drawn to methods for producing a construct encoding a single chain diabody library, and Claims 43 and 44 are interpreted as being drawn to a method for constructing an antibody library, where the methods require a "a linker of 30 to 150 base pairs comprising a cleavage site for a restriction enzyme", or b) a "linker of 30 to 150 base pairs comprising a cleavage site for a first restriction enzyme and a cleavage site for a second restriction enzyme that is different from, the first restriction enzyme", or c) "a linker of 30 to 150 base pairs comprising two or more cleavage sites for a restriction enzyme."
      The linker molecules in addition to being required to possess these structural characteristics must also upon translation into a peptide linker allow for the proper folding of the sc diabody or scFv for antigen binding. As taught by Volker et al. (Volkel (Protein Engineering 14(10):815-823 (2001); cited in the IDS of 5/25/06):
      "A scDb had a preferred length of 15 or more amino acid residues for the middle linker M and of 3-6 residues for the linkers A and B. No obvious bias towards a preferred linker sequence was observed. Reduction of the middle linker below 13 residues led to the formation of dimeric scDb, which most likely results from interchain pairing between all the V(H) and V(L) domains. Dimeric scDb were also formed by fragments possessing a long linker M and linkers A and B of 0 or 1 residue. We assume that these dimeric scDb are formed by intrachain pairing of the central variable domains and interchain pairing of the flanking variable domains."
      Therefore, the claims encompass a genus of molecules defined solely by its principal biological property, which is simply a wish to know the identity of any material with that biological property.

The specification teaches "a "linker" is not specifically limited as long as it does not interfere with expression of the antibody variable domains that are connected at both of its ends; the linker may or may not comprise restriction enzyme sites. Herein, a "long linker" means a linker of a size that enables the antibody heavy chain and light chain variable domains to be present as a scFv when the domains combined with the linker are expressed in a phage library. The length is not particularly limited, but preferably 30 bp to 150 bp, more preferably 36 bp to 90 bp, and most preferably 45 bp to 60 bp. Similarly, a "short linker" means a linker of a size that enables formation of a diabody (Db) when antibody heavy chain and light chain variable domains are combined with the linker and expressed. The length is not particularly limited, but preferably 6 bp to 27 bp, more preferably 9 bp to 21 bp, and most preferably 12 bp to 18 bp" [0058]; restriction sites are listed on p. 11, lines 8-12; and "For example, in the above case where BamHI and AccIII are used in a phage antibody library directed against antigens A and B, a fragment may be cut out using another restriction enzyme, such as SfiI, and inserted into an appropriate vector, as shown in FIG. 1" [0059]; and "For example, when phage libraries are constructed, two BamHI sites (underlined) can be designed within the linker, as below: TABLE-US-00002 GlyGlyGlyGlyGlySerGlyGlyGlyGlySerGlyGlyGlyGlySerGlyGlyGlyGlySer (SEQ ID NO: 3) GGTGGTGGTGGATCCGGTGGTGGTGGTTCTGGCGGCGGCGGCTCCGGAGGTGGTGGATCC (SEQ ID NO: 4)" [0080].

Accordingly, there is insufficient written description encompassing any one of the three linkers above because the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics are not set forth in the specification as-filed, commensurate in scope with the claimed invention. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

In the absence of structural characteristics that are shared by members of the genus of a "linker" of a), b) or c); one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicants allegations on pp. 9-15 of the Response of 1/13/09 have been considered and are not found persuasive. For purposes of brevity, their comments are excerpted as follows: Applicants allege based on the flow diagrams depicting the method of Claims 19 and 21 as presented in Exhibits A and B, respectively; the specification disclosure at paragraphs [0005, 0006, 0007, 0053, 0054, 0058, Figures 1 and 2); and the Volkel reference (Volkel, Protein Engineering 14(10): 815-823 (2001)), that the claims are fully supported for the method of making the diabody library using the instant claimed nucleotide linkers.

Response to Arguments

Each of the schematics in Exhibits A and B depicts what is an alleged optimum

embodiment for performing the method in order to produce a diabody. The examiner

reiterates what was discussed during the interview of August 28, 2008, namely, that the

linker length between, for example, "L1 and L2" and "H2 and H1" for element (e) of

Exhibit A (method of Claim 19), and the linker length between "L1 and L2" and "H2 and

H1" for element (e) of Exhibit B (method of Claim 21) is undefined in the instant claimed

method. Applicants have not demonstrated a structure/function correlation for the genus

of claimed linkers that would allow the proper translation and folding of each scFv in the

diabody in order to bind the respective target antigens.

It was further discussed during the interview, that the nucleotide linkers (30 to

150 base pairs) for any of the generic methods is required to a) have any restriction

enzyme site positioned anywhere in the linker for the L1-L-H1 scfv; and b) translate into

a linker of from _10 to 50 amino acids_. Thus, many possible scenerios for the first linker

of the L1-H1 scfv of any given diabody are encompassed by the claims. So for example,

when the L2-L2-H2 scFv is inserted into the L1-L1-H1 scFv, the linker on one side of the

L2-L2-H2 scFv can be a single amino acid while on the other side it can be nine amino

acids, e.g., (L1-(1aa L)-(L2-(L)-H2)-(9 aaL)-H1) _or_ (L1-(9aa L)-(L2-(L)-H2)-(1 aaL)-H1);

and myriad other possibilities are encompassed , e.g., (L1-(2aa L)-(L2-(L)-H2)-(8 aaL)-

H1) _or_ (L1-(8 aa L)-(L2-(L)-H2)-(2 aaL)-H1); (L1-(1 aa L)-(L2-(L)-H2)-(49 aaL)-H1) _or_

(L1-(49aa L)-(L2-(L)-H2)-(1 aaL)-H1); (L1-(2aa L)-(L2-(L)-H2)-(48 aaL)-H1) _or_ (L1-(48

aa L)-(L2-(L)-H2)-(2 aaL)-H1); etc. Applicants specification does not nearly define much

less support the total possible scenerios for the linkers of the instant claims because

Applicants did not contemplate the structure and function required for the myriad linkers.

Applicants did not contemplate the proper pair-wise association for the L1 and H1

domains in any given construct because the claims encompass linkers that would not

achieve this pairwise formation.

Further and under the Written Description Guidelines (66 FR 1099 (Jan. 5, 2001);

1242 O.G. 168 (Jan. 30, 2001) revised training materials from 3/29/08), the claimed

invention must meet the following criteria as set forth.

a) Actual reduction to practice: The specification discloses the linker is selected

"so long as it does not interfere with the expression of the antibody variable domains

that are connected at both of its ends" (p. 12, lines 7-10). The specification teaches

cloning and isolation of a diabody library using the polynucleotide linkers comprising :

SEQ ID NO:1- (p. 11);

SEQ ID NO:2- (p. 11); and

SEQ ID NO:4- (p. 18).

Finally, the specification teaches "Next, the phage library, or genes comprising

the variable domains prepared from the phage library (for example, phagemids)

concentrated from each library by panning and such, or genes amplified by PCR from

the above phage library), are treated with BamHI, and self-ligated *to reduce the length*

of the linker from 20 amino acids for scFvs to five amino acids, which is most suitable

for diabodies ("GlyGlyGlyGlySer (SEQ ID NO: 6)" encoded by "GGTGGTGGTGGATCC

(SEQ ID NO: 5)")." Thus the specification does not demonstrate making a diabody

library with just any polynucleotide linker of any composition and the length of 30 to 150

base pairs and having just any restriction site located anywhere in the linker.

b) Disclosure of drawings or structural chemical formulas: the specification and

drawings do not show that applicant was in possession of the genus of polynucleotide

linkers. The Exhibits A and B do not further define the structures of the linkers.

c) Sufficient relevant identifying characteristics: the specification does not identify

1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or

iv) functional characteristics coupled with correlation between structure and function for

the genus of polynucleotide linkers.

d) Method of making the claimed invention: the specification teaches the method

steps for making the diabody libraries using the linkers of SEQ ID NO: 1, 2 , 4 or 5.

e) Level of skill and knowledge in the art: the cloning of scfvs and generating

diabodies was well established at the time of the invention.

f) Predictability in the Art: the art does not appear to teach the myriad

polynucleotide linkers encompassed by the claims much less comprising just any

restriction site much less where in the linker the restriction site can be located, and

which can be properly expressed to allow for proper folding of the scfvs into a diabody

with antigen binding properties. Hudson et al. (J. Immunol. Methods 231:177-189

(1999); cited in the IDS of 5/25/06) teaches that "A precise definition of the N- and C-

terminal residues of the V-domains is required when designing the linker length" (p. 180,

Col. 1, ¶ 1). A linker of 5 residues favors the folding of scfv as a diabody (Rousch et al.,

Br. J. Pharmacol., 125: 5-16 (1998)).

Applicants have not demonstrated with sufficient evidence the genus of

polynucleotide linkers of 30 to 150 base pairs having any restriction site located

anywhere within the linker and which translate to permit the expression and folding of

the scfvs into a diabody format with retention of binding for the respective antigens. The

ordinary artisan could reasonably conclude that Applicants were not in possession of

the claimed genus of polypeptide linkers at the time of application filing.

In response to applicant's argument that the specification and Volkel reference

show certain features of applicant's invention, it is noted that the features upon which

applicant relies (i.e., nucleotide linkers of SEQ ID NOS: 1, 3 and 5) are not recited in the

rejected claim(s). Although the claims are interpreted in light of the specification,

limitations from the specification are not read into the claims. See *In re Van Geuns*, 988

F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The rejection is maintained.

New Grounds for Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all

obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set
> forth in section 102 of this title, if the differences between the subject matter sought to be patented and
> the prior art are such that the subject matter as a whole would have been obvious at the time the
> invention was made to a person having ordinary skill in the art to which said subject matter pertains.
> Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148

USPQ 459 (1966), that are applied for establishing a background for determining

obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 19-22 and 31-34 are rejected under 35 U.S.C. 103(a) as being

unpatentable over Little et al. (CA 2331641 or DE19819846; published 11/11/99; both

cited in the IDS of 5/25/06) in view of McGuinness et al. (Nat. Biotech. 14:1149-1154

(1996); cited in the PTO 892 form of 8/8/07) and Volkel (Protein Engineering

14(10):815-823 (2001); cited in the IDS of 5/25/06).

The interpretation of the claims is of record.

The claims were prima facie obvious at the time of the invention in view of Little,

McGuinness and Volkel.

See Figure 2 of Little (DE19819846), where Little shows restriction digestion of a

first linker in a first scfv; restriction digestion of a second linker in a second scfv and

recombining the VH1-VL2 and the VH2-VL1 constructs into a single fused scfv diabody

construct for producing libraries.

McGuinness discloses methods for constructing an antibody phage display

library where the V regions from antibodies against the hapten phOX or Dig are

constructed into two pools of scFvs repertoires having a 15-amino acid linker between

each VH and VL domain, where the orientation of the domains is VH-linker-VL (p.

1150, Col. 1, ¶1). The scFv pools were recombined into a diabody format: VHA-VLB-rbs

(linker)-VHB-VLA, where the linker between each VH and VL domain was "shortened"

to a zero linker (p. 1150, Col. 2, ¶1) using one of two methods: ligation mediated

assembly or cassette cloning where the final diabody is inserted into an expression

vector. For ligation-mediated assembly, a two- (Fig 21, A-C) or three-step (Fig. 2iD)

process is taught in the Materials and Methods on p. 1153, ¶2. In the three-step

approach, an 800 bp fragment comprising Dig VH-phOxVL and phOxVH fragment are

cut with a restriction enzyme and ligated, then the ligated fragment was mixed with a

Dig VL fragment and digested with another restriction enzyme, and then ligated to

produce the diabody insert. The two-step approach comprised taking the 800 bp

fragment comprising Dig VH-phOxVL and phOxVH and a phOxVH-DigVL fragment,

ligating the mixture and digesting with restriction enzymes to produced the diabody

insert. For cassette cloning, VHA-VLB and VHB-VLA fragments were generated by PCR

extension from the scFv pools, and the fragments digested with different restriction

enzymes (Fig. 2ii) to produce a DigVH-phOxVL fragment and a phOxVH-DigVL

fragment with terminal restriction sites followed by assembly into the diabody (p. 1151,

Col. 1, ¶2; and M & M, p. 1153, Col. 2, ¶2). The 15 amino acid linker of McGuinness is

considered as reading on the linker for the first and second single scFvs and the HV

and LV. The claims are not drawn to the specific order in which the VH1 and VL1 or the

VH2 and VL2 should occur. In other words, McGuinness teaches a diabody format:

VHA-VLB-rbs (linker)-VHB-VLA which reads on the instant claims. Thus McGuinness

teaches at least two possible methods for producing a scfv diabody format or construct,

but more importantly, that the ordinary artisan could predict that scfv diabody libraries

were producible at the time of the invention much less functional based on McGuinness.

Volkel discloses constructing a diabody phage display library comprising single

chain diabody CEA scFv/Gal scFv constructs with a randomized middle linker from

where the M linker is of variable length and comprises at least one restriction site (See

Figure 2A and B). Volkel discloses generating a fragment comprising GalVL-M linker-

GALVH where the M linker comprises a restriction site and subcloning the fragment into

the linker region for the CEA scFv where the linker region comprises two restriction

enzyme sites, BstE II and Sac I. Volkel discloses generating clones with variable linker

and M-linker lengths and comprising different amino acid sequences (Tables III and IV)

which are cloned into an expression vector.

One skilled in the art would have been motivated and been assured of

reasonable success in having produced the instant methods at the time of the invention

based on the combined disclosures of Little McGuinness and Volkel because each

disclose the technology for constructing single-chain diabody phage display libraries

where a scFv recognizing a first antigen comprising a linker with a restriction enzyme

site and a second scFv recognizing a second antigen comprising a linker are treated

with a restriction enzyme in order to obtain fragments which are then ligated in order to

construct a final fragment having the VH and VL domains against the second antigen

inserted between the VH and VL domains against the first antigen are assembled into

the diabody phage display library. Each of the references discloses techniques involving

differential restriction enzyme digestion of various fragments and the technology for

selective insertion of the VH2/VL2 or VL2/VH2 pair between the VH1/VL1 or VL1/VH1

domains to generate a phage display diabody library. Each of the references teaches

obtaining fragments comprising variable domains and shortening the linker between the

domains in a ligation (PCR extension step). Further because the instant claimed method

actually involves even fewer steps than taught by any of the reference disclosures in

order to generate a scfv diabody construct, the ordinary artisan would have been

motivated to obtain a process that was ensured to generate functional scfv diabody, by

inserting a sequence encoding a second pair of heavy and light chain variable domains

into the open restriction site for the linker of a first pair of heavy and light chain variable

domains.

Based on the combined reference disclosures, one skilled in the art could have

been assured of success in introducing linkers between VH and VL domains comprising

restriction sites for subcloning into or between VH and VL domains against a different

antigen because the references taught that subfragments could readily be generated

and where a VH/VL pair against one antigen was inserted between the VH and VL

against a different antigen. Little and McGuinness teach that construction and selection

from such a library is possible and it avoids unfavorable combinations (p. 1153, Col. 1,

¶2), and Volkel discloses generating single-chain diabodies with optimized linker

sequences and expressed by phage display where correctly folded molecules can be

screened against a variety of different target cells and antigens (p. 822, Col. 2, ¶3).

Further, one skilled in the art could have readily constructed a self-ligating antibody

library based on the method steps of Little, McGuinness and Volkel to produce a second

library having a shorter linker in relying on restriction enzyme sites in linker to restrict

out a certain length of the linker to obtain a shorter linker.

Under the recent KSR decision, the cited references of art are not required to

"*explicitly* teach or suggest" all of the method steps. The Supreme Court has determined

in *KSR International Co. v. Teleflex, Inc.*, 550 U.S._, 82, USPQ2d 1385 (2007), that "a

person of ordinary skill attempting to solve a problem will" not " be led only to those

elements of prior art designed to solve the same problem........." (KSR, 550 U.S. at_,

82 USPQ2d at 1397). In addition, the court found that "When a work is available in one

field of endeavor, design incentives and other market forces can prompt variations of it,

either in the same field or a different one. If a person of ordinary skill can implement a

predictable variant, 35 USC 103 likely bars its patentability" (KSR, 550 U.S. at_, 82

USPQ2d at 1396). Further the court found that the Federal Circuit has erred in applying

the teaching-suggestion-motivation test in an overly rigid and formalistic way, in

particular by concluding "that a patent claim cannot be proved obvious merely by

showing that the combination of elements was 'obvious to try'" (KSR, 550 U.S. at_, 82

USPQ2d at 1397) and has further determined that ".......[t]he combination of familiar

elements according to known methods is likely to be obvious when it does no more than

yield predictable results" (KSR, 550 U.S. at_, 82 USPQ2d at 1395). The court further

found that "......... the conclusion that when a patent simply arranges old elements with

each performing the same function it had been known to perform and yields no more

than one would expect from such an arrangement, the combination is obvious" (KSR,

550 U.S. at_, 82 USPQ2d at 1395-1396). *Thus, when considering obviousness of a*

combination of known elements, the operative question is "whether the improvement is

more than the predictable use of prior art elements according to their established known

use."). Thus in general, the combined art reference disclosures teach that the skilled

artisan could reasonably predict inserting a sequence encoding a second pair of heavy

and light chain variable domains into the open restriction site for the linker of a first pair

of heavy and light chain variable domains, would produce a library of functional

diabodies. It is the examiner's position that Applicants have not provided an

improvement over the combination of known elements already disclosed in the prior art

at the time of the invention.

Conclusion

10.   No claims are allowed.

11.   Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883.

The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for

the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the

Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information

system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Examiner, Art Unit 1643
Partial Signatory Authority